REMARKS

New claims 17-19 have been added to the specification. Support for new claims 17-19 may be found in originally pending claims 7-9. New claims 17-19 in no way add new matter to the specification. As such, entry and consideration thereof are respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-4 have been rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Specifically, the Examiner asserts that the specification is enabled for a method of generating the SH3 domain of the Hck RT-loop, but not enabled for methods of generally generating SH3 domains of RT-loops by replacement with any amino acid residue. The Examiner asserts that the specification fails to provide guidance for extrapolating the specific example of generating the SH3 domain of the Hck RT-loop to other SH3 domains. The Examiner bases the inability to extrapolate to other SH3 domain on the issues of unpredictability in size and sequence of RT loops; the correct peptide length a particular vector can display etc.

The Examiner also relies on the teaching in the specification that binding of SH3 to the Nef ligand is highly dependent on the amino acids flanking the core sequence, but that there is as yet no known ligand binding motif for the binding site. The Examiner asserts that it is not conclusively known

whether proline-rich peptides are true SH3 ligands because of the amino acid differences in the SH3 receptor sites. The Examiner asserts because of these factors it would require undue experimentation to determine what amino acids of a particular SH3 are responsible for ligand binding or to determine a method generally applicable to all SH3 domain-containing proteins.

Applicants traverse this rejection and withdrawal thereof is respectfully requested. The Examiner asserts that the lack of common sequence motif in the RT-loops creates unpredictability in the present invention. However, the Examiner appears to have misunderstood the nature of the invention. As discussed on pages 3-5 and 9 of the specification, it has been shown that the binding specificity of SH3 domains to the ligands is dependent on the non-conserved regions of the RT-loop. The Examiner is correct that there as yet is no common motif identified for the non-conserved regions of the RT-loop involved in ligand binding. However, while the sequences of the RT-loops flanking the conserved core structure differ in specific amino acid sequences, they share the common role of determining ligand binding specificity. The method of the present invention is not dependent on the specific amino acid sequence of the RT-loop. The present invention depends on the common feature of SH3 domains that ligand specificity is determined by the RT-loop, whatever the amino acid sequence may be. Thus, the present method is applicable to any SH3 domain. The specific amino acid

sequence of the RT-loop does not need to be known because with the present method randomized RT-loop domains are generated. While the specific sequences of the RT-loops are not common among different SH3 domains, the location and function of the RT-loops is common and thus, the presently claimed method is generally applicable to any SH3 domain.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-4 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite.

More specifically, claim 1 has been rejected as being unclear as to the difference between steps a) and b).

Claim 1 has been further rejected as being indefinite regarding step c) with the assertion that step c) recites, "identify" whereas the preamble recites, "generating."

Finally, claim 1 has been rejected for recitation of the terms "novel" and "tailored."

Claim 2 has been rejected for recitation of "is effected" because of a failure to recite how the replacement of amino acids is effected. Claim 2 has been further rejected as lacking antecedent basis for "The variable region of the RT-loop."

Claim 3 has been rejected for lacking antecedent basis for "the six amino acids" and for being unclear in the recitation of "corresponding."

Claim 4 has been rejected as being indefinite in the recitation that the recombinant libraries are selected from plasmid, phagemids and viral libraries, with the assertion that it is not clear if plasmids, phagemids and viral are vectors or libraries.

Claims 1-4 have been amended to address and clarify the claims. These amendments in no way affect the scope of the claims because no element of the claims have been in any way narrowed. For example, the claims have been amended to provide proper antecedent basis for all terms. In addition, claim 1 has been amended to delete the term novel and consistently recite "generate." Claim 1 has been further amended to replace the more colloquial term of "tailored binding properties" with "desired ligand binding properties." As these amendments address and overcome the rejections under 35 U.S.C. §112, second paragraph and clarify the claims, withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. §102(a)

Claims 1-4 have been rejected under 35 U.S.C. §102(a) as being anticipated by Hiipakka et al. More specifically, the Examiner asserts that Hiipakka et al. disclose beginning on page 1097, column 2, the presently claimed method of producing SH3 domains by producing a recombinant library that expresses a mutant RT-loop domain of the SH3 regions and affinity selecting

the SH3 domains. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

The effective prior art date of Hiipakka et al. is November, 1999. The present invention, claims priority under 35 U.S.C. §119(e) to U.S. provisional application No. 60/136,085, having a priority date of May 26, 1999, a copy of which is attached hereto. U.S. provisional application No. 60/136,085 provides full support for the invention of claim 1. As such, Hiipakka et al. is not prior art against the present invention and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §102(b)/103

Claims 1-4 have been rejected under 35 U.S.C. §102(b) or §103 as being anticipated by or obvious over Lee et al. (EMBO Journal). More specifically, the Examiner asserts that Lee et al. disclose a method of producing an SH3 domain from the RT-loop of different SH3 domains by first mutating the RT-loop and obtaining a collection of RT-loop mutants from a library of cDNA. The mutated RT-loop is then affinity purified by binding to the PXXP motif of Nef. The Examiner asserts that the different mutations of the SH3 domains of the kinases of Lee et al. is the same as the randomized RT-loop domains of the present invention or, alternatively, that it would have been obvious to make the different mutations into a randomized collection.

Applicants traverse this rejection and withdrawal thereof if respectfully requested. The present invention, as encompassed by claim 1, is drawn to a method for generating artificial SH3 domains having desired ligand binding properties, by a) producing a collection of SH3 domains that contain randomized RT-loops (RRT-SH3 domains), b) generating recombinant libraries containing the RRT-SH3 domains, and c) subjecting the libraries to affinity or functional selection steps to generate the artificial SH3 domains.

In Lee et al. the RT-loop of Fyn-SH3 was modified to resemble the Hck-SH3. Thus, Lee et al. do not disclose the generation of randomized new sequences for RT-loop domains, rather they simply replace the RT-loop of Fyn-SH3 with another naturally occurring RT-loop sequence, that of Hck-SH3. The procedure disclosed in Lee et al. would not have been possible without previously knowing the sequence of Hck-SH3. Thus, Lee et al. are merely mimicking the naturally occurring binding of Hck-SH3. However, as discussed on page 5, lines 6-21, the present inventors have found that by using the presently recited method of random generation of the RT-loop sequence combined with affinity selection, instead of merely mimicking known SH3 domains, one can generate SH3 domains with specifically desired binding properties, such as unnaturally high affinity for specific proteins. There is no disclosure or suggestion in Lee et al. of a means of generating any but naturally occurring SH3

binding domains. There is no disclosure in Lee et al. of a method of generating artificial SH3 domains having desired binding properties. As such, the present invention is neither anticipated by nor obvious over Lee et al. Withdrawal of the rejection is respectfully requested.

As the above-indicated amendments and remarks address and overcome the rejections of the claims, withdrawal of the rejections and allowance of the claims are respectfully requested.

Should the Examiner have any questions regarding the present application she is requested to please contact MaryAnne Armstrong, PhD (Reg. No. 40,069) in the Washington DC area at (703) 205-8000.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $195.00 is attached hereto.

A marked up version showing amendments to the specification and claims is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly, extension of time fees.

Respectfully submitted,

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MARKED-UP VERSION SHOWING CHANGES

The claims have been amended as follows.

1. (amended) A method for generating **artificial** SH3 domains **having desired ligand** ~~with tailored~~ binding properties, **which comprises:** ~~comprising~~

a) producing a collection of **DNA fragments encoding** SH3 domains containing a randomized RT-loop (RRT-SH3 domains),

b) generating recombinant libraries **comprising** ~~expressing~~ said RRT-SH3 domains, **and**

c) subjecting ~~such~~ **said** libraries to affinity or functional selection steps to ~~identify novel~~ **generate artificial** SH3 domains.

2. (amended) The method according to claim 1, wherein step a) **comprises** ~~step a) is effected by~~ replacing amino acid residues in ~~the~~ **a** variable region of the RT-loop ~~by~~ **with a random combination of** any other amino acid residues.

3. (amended) The method according to claim 2, wherein ~~said~~ **the** amino acid residues in the variable region of the RT-loop **that are replaced comprise** ~~are the~~ six amino acid residues ~~corresponding~~ **that immediately follow a conserved stretch of amino acids having an ALYDY (SEQ ID NO:1) consensus sequence** ~~to~~

~~the residues 69 to 74 (SEQ ID NO: 5) in the human Hck protein sequence~~.

4. (amended) The method according to claim 1, wherein the recombinant libraries ~~are selected from~~ **comprise said RRT-SH3 domains in** plasmid, phagemid **or** ~~and~~ viral **vectors** ~~libraries~~.

New claims 17-19 have been added.